APPENDIX 5

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VOLUME 66 JULY-DECEMBER, 1953

THE C. V. MOSBY COMPANY ST. LOUIS 1953

DOES THE ADMINISTRATION OF DIETHYLSTILEESTROL DURING PREGNANCY HAVE THERAPEUTIC VALUE? †

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(From the Department of Obstetrics and Gynecology of the University of Chicago and the Chicago Lying in Hospital)

IN 1946 Smith and Smith' suggested that increasing amounts of disthylstil, bestrol should be administered to all women during pregnancy to prevent or decrease the hazards of the late complications of pregnancy for mothers and babies. The basis for such prophylactic therapy as well as the active therapy of these pregnancy complications stems from a series of experiments by the Smiths on the steroid hormones in normal and abnormal pregnancy. These laboratory observations and their theoretical implications were supported by clinical observations, part of which were made under the supervision of the Smiths and part were the collected reports of other clinical observers.

The use of diethylstilbestrol to prevent and to treat pregnancy complications is based on the supposition that there develops a deficiency in the production of progesterone and other steroids by the placenta which predisposes to or causes these pregnancy complications. The secretion of these steroids can be stimulated by diethylstilbestrol. The increased amounts of steroids made available by the placenta postpone, reduce the severity of, or prevent some of the late complications of pregnancy.

The laboratory experiments which provided the background for this interesting concept of the Smiths have lacked confirmation by other investigators. Davis and Fugó' in two reports noted that the administration of diethylstilbestrol to patients during pregnancy did not result in an increased output of urinary pregnanediol, a measure of progesterone metabolism. Sommerville, Marrian and Clayton' confirmed these observations and noted a drop in urinary pregnanediol and no gross change in endogenous estrogen. Although many additional experimental data will be necessary to determine the role of diethylstilbestrol in placental steroid metabolism, this paper will confine itself, to the clinical implications of the Smith concept.

Smith and Smith in 1949 reported on the influence of diethylstilbestrol on the progress and outcome of pregnancy in a series of primigravidas. As

This investigation was supported in part by a research grant PHS RG2570, from the National Institutes of Realth, Public Health Service.

1Presented at the Seventy-sixth Annual Meeting of the American Cynecological Society,
Lake Placid, N. Y., June 15 to 17, 1951.

Volume 60 Number 6

controls they used a They recorded the f the late toxemias of usually large for th was decreased. (4) decreased. (5) The r

The most serious Patients to whom to meticulous study and ously. In two nutrit tients who were coor instructions, keep godence of abortion, pralower perinatal deswomen delivered con were compared with received identical tre significant differences

The prophylactic use in pregnancy com to postpone, or to an mothers and babies is plished by the daily or a careful perusal of a not supported by adeq

The properly conshould have no knowl of patients should rethe medication on tritreated simultaneously cently reported by F that diethylstilbestrol maturity, perinatal mo

We felt that it w clinical experiment to practice. The first pa study terminated Nov.

The following crilarge so that the resuof patients who were uwas decided that 2,000 prior to the twentieth Every other patient, wsonal element, each prindividual who was no

Since our data were at variance with those of the Smiths, they were all rechecked. The charts of patients with toxemia of pregnancy, premature delivery, stillbirths and neonatal deaths, and any other complication or abnormality, were examined again by one of the senior authors with no knowledge of the kind of medication. There was no significant change in any of the

TABLE IX. CONGENITAL ANOMALIES

TYPE OF ANOMALY	PRIMIPARAS							. MULTIPLEAS .						
	STILBESTROL			not.	CONTROL '			STUBESTROL				CONTROL		
`Minor	,	•	. 7			7			9				4	,
Skin, as papilloma			7			16 .		•	- 1 ,		•	*	ő	1.5
Cystocele, hydrocele			4			3 -			3			•	5	£
Harenp, clert palate, etc.			1			0			0				· 1,	
Clubfeet, multiple digits			2	•		ຸ 5			5				21	
Mongolism			0			0			ø				1	
Brain and spinul cord	- 4		. I			- 0			, 0				0	
Cardine, etc.	2.		2			1 :			Į.		r : .*		2	
Gastrointestinal			1			. 0		· . ·	. 0				0	
"Genitourinary		` `,	, G		•	2 .		•,,,•	0	. *			-3	<:
dfultiple major		٠.,	. 2	***		2		·	_1				- 3	-
Total anomalies	, ,		27			32			27	•	3.		24	
Total infants			426			415			375,		•		361	`

Conclusions

A strictly controlled clinical trial of the therapeutic value of diethylstilbestrol administered to patients during pregnancy in reducing the hazards; of some of the late complications of pregnancy for mothers and babies has been reported.

The various complications were studied in the total unselected group of patients divided into primigravidas, primiparas, and multiparas. Then the groups were again studied after all groups were corrected to compare with

The results of the administration of diethylstilbestrol to \$40 patients according to a schedule suggested to Smiths were compured with the results of an identical placebo to given to 806 patients. Stilbestrot did not reduce the incidence of abortion, prematurity, or postmaturity. Premature babies of stilbestrol-treated mothers were no longer nor. more mature for their gestational ages than comparable prematures in the control group of placebo treated mothers. It did not decrease the incidence of perinatal mortality. It did not decrease the frequency of the toxemias of: pregnancy.

Acknowledgment is made to Eli Lilly and Company for aid in making the stillbestrot and placebo tablets with the dye and for the final determination of the stilbestrol; to Lillian Natusko for the examination of the urines for phenol red; to the staff and residents for their cooperation.

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- М. Т.,
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- 10. Perguson, J.
- 11. Canario, E. b

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"... Wo_also wis that the only diff groups lay in the tancher, who saw dentally, fully an drawal in patient: conveyed this con Dr. Oliva Smith, t Actually, most of s and, therefore, ma

Neither the patients was set c omitted from our those who had thr our control series. mbo began taking phylactic value of Sprevious abortious peatedly misearry mow are certain th ing abortion, there

They include There were more a (11 .ev 22), ilors pre-eclimpsia.